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ABDOMINAL AORTIC ANEURYSM

GENDER ASPECTS ON RISK FACTORS AND TREATMENT

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*The whole of science is nothing
more than a refinement of
everyday thinking*
Albert Einstein

***Till
Tage och Sonja***

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ABSTRACT

Abdominal Aortic Aneurysm (AAA) is a common condition in the Western world and an important cause of sudden death. Recent research emphasizes that although women are inherently less likely to develop AAA, those who do develop AAA seem to have a more unfavorable aneurysm disease than men with higher rupture risk and higher standardized mortality ratio after intervention. Despite previous efforts to elucidate gender differences in patients suffering from AAA it is obvious that further research is necessary. This thesis is based on four studies focusing on different gender aspects of patients with AAA.

The first study is a population-based investigation of temporal trends in number of interventions performed for AAA and outcome in Sweden 1990-2005. The study included 14369 patients. Interventions for non ruptured, but not for ruptured AAA increased over time. Among patients treated for non ruptured AAA an expected rapid increase of endovascular repair was observed. The male to female ratio did not change during the study period. We did not find any gender differences in postoperative mortality after adjustment for age.

In the second study the risk of AAA associated with positive family history was assessed. This is the first population-based case-control study within this field. 3183 AAA cases and 15943 age, gender, and region matched controls were included. We were able to demonstrate that the relative risk associated with a positive family history of AAA was approximately doubled (odds ratio 1.9; 95% confidence interval 1.6-2.2). We did not find any influence of gender.

In the third study the prevalence of Thoracic Aortic Aneurysm (TAA) in patients diagnosed with AAA was investigated. AAA patients attending the out-patient clinic at Karolinska University Hospital who had been examined with an abdominal and thoracic Computer Tomography (CT), were included (n=354). We found that approximately one quarter had a concurrent TAA, using gender specific criteria. Women were particularly affected, 48% compared to 23% in men ($p<0.0001$).

The fourth study attempted to widen the understanding of the higher rupture risk in women with AAA compared to men by investigating this difference from a biomechanical perspective. Several studies have shown that Peak Wall Stress (PWS) and Peak Wall Rupture Risk (PWRR), predicted by a Finite Element (FE) analysis of AAA derived from CT, is a better predictor of rupture than AAA diameter. PWS and PWRR were estimated for 15 men and 15 women with AAA. Women were analyzed with "female wall properties" and with "male wall properties". PWS was similar, whereas PWRR was slightly higher among women. When female patients received "male wall properties", no difference in mean PWRR between women and men was found. The results suggest that geometrical properties alone do not explain the previously reported higher rupture risk for female AAA patients, more likely differences in biomechanical properties could contribute.

Although obvious gender differences in AAA patients exist, this thesis also reveals several similarities. The studies point out the need of future research in order to optimize the care of AAA patients.

LIST OF PUBLICATIONS

This thesis is based on the following papers, which will be referred to by their Roman numerals as indicated below:

- I. **More patients are treated for nonruptured abdominal aortic aneurysms, but the proportion of women remains unchanged.**
Emma Larsson, Fredrik Granath, Jesper Swedenborg and Rebecka Hultgren
Journal of Vascular Surgery. 2008;48:802-7
- II. **A population-based case-control study of the familial risk of abdominal aortic aneurysm.**
Emma Larsson, Fredrik Granath, Jesper Swedenborg and Rebecka Hultgren
Journal of Vascular Surgery. 2009;49:47-51
- III. **High frequency of thoracic aneurysms in patients with abdominal aortic aneurysms.**
Emma Larsson, Lia Vishnevskaya, Bo Kalin, Fredrik Granath, Jesper Swedenborg and Rebecka Hultgren
Annals of Surgery.
[Epub ahead of print] DOI: 10.1097/SLA.0b013e3181d96498
- IV. **Analysis of aortic wall stress and rupture risk in AAA patients with a gender perceptive.**
Emma Larsson, Fausto Labruto, T. Christian Gasser, Jesper Swedenborg and Rebecka Hultgren
Submitted

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LIST OF ABBREVIATIONS

AAA	Abdominal Aortic Aneurysm
ADAM Trial	Aneurysm Detection and Management Trial
CI	Confidence Interval
CT	Computed Tomography
EVAR	Endovascular Aneurysm Repair
FDR	First Degree Relative
FE	Finite Element
ICD	International Classifications of Diseases
ILT	Intraluminal Thrombus
MAP	Mean Arterial Pressure
MMP	Matrix Metalloproteinase
MRI	Magnetic Resonance Imaging
NBHW	National Board of Health and Welfare
OR	Odds Ratio
OVER Trial	Open Versus Endovascular Repair Trial
PWRR	Peak Wall Rupture Risk
PWS	Peak Wall Stress
SMR	Standardized Mortality Ratio
SWEDVASC	Swedish National Registry for Vascular Surgery
TAA	Thoracic Aortic Aneurysm
UKSAT	United Kingdom Small Aneurysm Trial

INTRODUCTION

The reasons for the marked male predominance in the prevalence of AAA remain unresolved.^{1, 2} The delayed onset of AAA in women may indicate that estrogens contribute to reduce the prevalence of AAA in women.^{3, 4} Efforts to clarify gender differences in patients suffering from AAA have been made the last years, but it is obvious that several questions remain to be answered. Men are more likely to develop AAA but appear to have a less aggressive disease with lower rupture risk⁵⁻⁷ and lower standardized mortality ratio after intervention^{8, 9} compared to women. Despite previous well known differences between men and women with AAA, limited data are available in order to fully understand the contributing factors.

This thesis, based on four studies, attempts to elucidate some of the gender aspects of patients with AAA. In study I, we investigated temporal trends regarding number of procedures performed for AAA in Sweden the last decades and outcome with special focus on gender differences. Study II is the first population-based case-control study investigating the risk of AAA associated with a positive family history of AAA and possible gender differences. In study III our main objective was to investigate the prevalence of TAA in patients with AAA and a secondary objective was to investigate a possible association with gender. Study IV is a pilot study investigating biomechanical differences between men and women with AAA.

New knowledge obtained from this thesis will hopefully contribute to improved identification of risk factors for AAA and enhanced management of patients with AAA, but also encourage further research.

BACKGROUND

HISTORICAL REMARKS

The first written description of aortic aneurysm is probably found in the “Eber Papyrus” of about 1500 BC, which is one of the oldest preserved medical documents. It states that only magic could cure tumors of the arteries, most likely referring to aneurysms.¹⁰ In the beginning of the 19th century the first ligation of the abdominal aorta was performed¹⁰ and about 100 years later the first ligation of an Abdominal Aortic Aneurysm (AAA).¹¹ One of the most famous patients suffering from AAA is Albert Einstein. In 1948 he underwent a laparotomy where an AAA was found to be the cause of his abdominal pain. The aneurysm was wrapped with cellophane, a tissue irritant causing fibrosis, and Einstein was discharged 3 weeks later. However, at the age of 76 Einstein died due to rupture, refusing surgery with the words “I want to go when I want. It is tasteless to prolong life artificially. I have done my share, it is time to go, I will do it elegantly”.¹²

In the middle of the 20th century aortic homografts were introduced. The first successful surgical resection of an AAA, offering durable protection from aneurysm rupture, is attributed to the French surgeon Charles Dobust in 1951.¹³ A rapid development followed during the next decades. In the 1950s homografts were replaced by synthetic grafts, introduced by Voorhees¹⁴, and knitted Dacron described by DeBakey in 1958.¹⁵ In the early 1990s Volodos in the Ukraine and the Argentinean surgeon Parodi introduced endovascular technique for aneurysm repair.^{16,17}

DEFINITION

The word aneurysm is derived from Greek “aneurusma” meaning widening. An aneurysm involves all layers of the vessel wall and is called fusiform if the whole circumference of the artery is affected, or saccular if it involves only a part of the circumference. Aortic aneurysms occur in several different localizations, most frequently in the infrarenal abdominal aorta. An aneurysm has been defined as a “permanent localized dilatation of an artery having at least a 50% increase in diameter compared with the expected normal diameter of the artery in question”.¹⁸ This definition requires knowledge of normal vessel dimensions. Several parameters such as male gender, increasing age and large body surface area have been reported to be associated with variations in the infrarenal¹⁹⁻²¹ and suprarenal aortic diameter.²¹⁻²³ Relative aortic diameter based on the predicted size in relation to body surface area is reported to be larger in women than in men.²⁴ A recently published study presented normal aortic dimensions and

suggested cut off lines for AAA and TAA in 70 year old men and women.²⁵ Women had smaller aortic dimensions in all segments compared to men. Table 1.

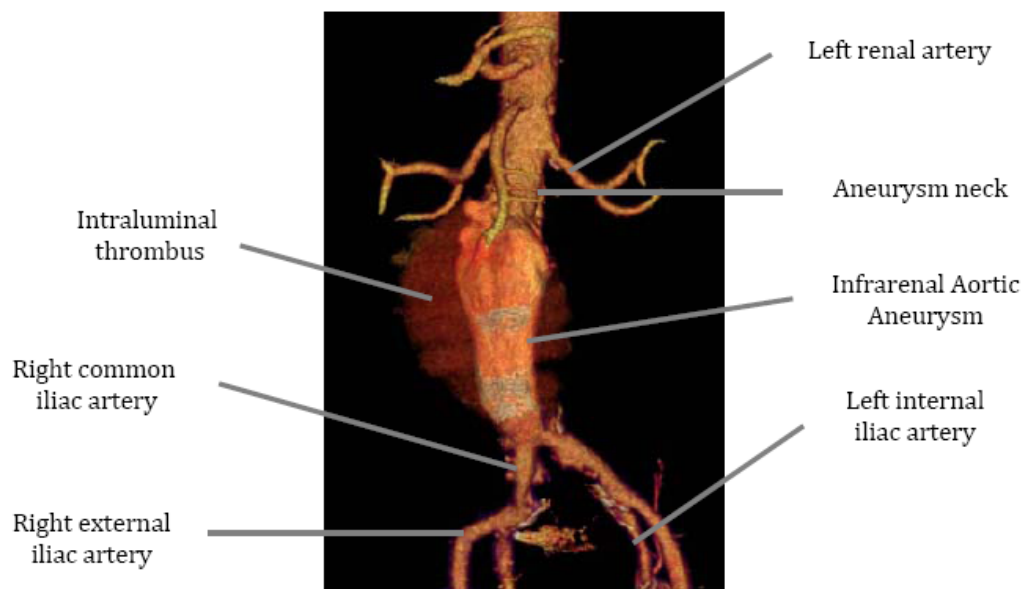
Table 1. Normal aortic dimensions in 70-year old men and women

Segment	Men	Women
Ascending thoracic aorta	40 mm	34 mm
Descending thoracic aorta	32 mm	28 mm
Largest infrarenal abdominal aorta	24 mm	22 mm

Adapted from Wanhainen et al²⁵

An AAA is generally defined as an aortic diameter ≥ 30 mm. This definition is currently used in Sweden in clinical practice for both men and women, and is partly based on data from the Aneurysm Detection and Management (ADAM) trial²⁶ and the United Kingdom Small Aneurysm Trial (UKSAT).²⁷ This definition is also used in the United States according to the “Guidelines for screening of AAA” from the US Department of Health and Human Services.²⁸ See figure 1 for illustration of an infrarenal AAA.

Figure 1. Infrarenal AAA



THE ARTERIAL WALL

Arteries consist of three layers. Tunica intima is the innermost layer and is composed of a single layer of multifunctional endothelial cells. Tunica media is the middle layer and consists of layers of smooth muscle cells in close connection with elastin and collagen fibers. The aorta and its proximal large branches are called *elastic* arteries due to the prominence of elastic fibers in the wall, whereas smaller arteries are named *muscular* due to a higher content of smooth muscle cells and less collagen and elastin. Tunica adventitia, the outer layer, consists of fibrocellular connective tissue and it also contains a network of vasa vasora.²⁹ The thoracic and the abdominal aortas are both elastic arteries but differ in their biomechanical properties and the origin of smooth muscle cells.³⁰ The infrarenal aorta is normally devoid of vasa vasora. In aneurysms, however, neovessels form as a part of the inflammatory reaction.³¹

PATHOGENESIS

Patients with AAA and patients suffering from atherosclerosis have similar risk factor profiles, but the pathogenesis is different.^{32, 33} An aneurysm is mainly a disease of the media and adventitia of the vessel wall, whereas atherosclerosis primarily affects the intima. Atherosclerotic lesions are thickenings of the intima and are preceded by an accumulation of cells with high lipid content underneath the endothelium, a so-called fatty streak. The lesions consist of connective tissue elements, lipids, debris and cells including inflammatory cells, endothelial and smooth muscle cells. Inflammatory and immune cells constitute an important part of the lesion, or atheroma.³⁴ In AAA formation, transmural inflammation, destruction of the extracellular matrix by various proteases and impairment of its reconstruction seems to be fundamental.^{35, 36} The histopathological changes in AAAs are particularly evident within the elastic media, which normally is dominated by smooth muscle cells and the pathological processes are associated with smooth muscle cell depletion.³⁷ Destruction of elastin and collagen by matrix metalloproteinases (MMPs) and other proteolytic enzymes has been shown to be crucial in formation of an AAA.³⁸⁻⁴⁰

Aortic aneurysms are associated with atherosclerosis to a lesser extent in the thoracic compared to the abdominal aorta.⁴¹ There are several additional differences between AAA and thoracic aortic aneurysm (TAA): vascular smooth muscle cell pathology is secondary in AAA and primary in TAA, an intraluminal thrombus (ILT) is often present in AAA but not in TAA and inflammatory processes are different.^{30, 42}

EPIDEMIOLOGY: PREVALENCE, INTERVENTION AND ADMISSION

Prevalence

AAA is a disease with a skewed gender distribution. Four well known randomized population-based studies investigating the benefit of screening of AAA have been

published; the Chichester study⁴³ and the Multicenter Aneurysm Screening Study⁴⁴ from the UK, the West Australian Screening Study⁴⁵ and the Viborg Study from Denmark.⁴⁶ The overall prevalence of AAA in these studies was approximately 4-7%.

In the Chichester study, a screening study of a population 65-80 years of age, 1.3% of the women and 7.6% of the men had an AAA.⁴³ This corresponds well the prevalence and to the male to female ratio in a study of US veterans⁴⁷ and the population-based Rotterdam study.¹ In a Norwegian screening study of men and women aged 25-84, 2.2% of the women had an AAA compared to 8.9% of the men.⁴⁸ These studies are summarized in table 2.

Table 2. Prevalence of AAA

Study Setting	Age	Study Population (N)		Prevalence	
		Men	Women	Men	Women
Chichester, UK ⁴³	65-80	2342	3052	7.6%	1.3%
ADAM screening program, US ⁴⁷	50-79	122272	3450	4.3%	1.0%
Rotterdam, The Netherlands ¹	≥55	2217	3066	4.1%	0.7%
Tromsø, Norway ⁴⁸	25-84	2962	3424	8.9%	2.2%

Gender distribution regarding prevalence and incidence among AAA patients differ from TAA patients. Women constitute a larger proportion among TAA patients compared to AAA patients. In a report including both aneurysms and dissections of the thoracic aorta, an approximately 2 to 1 male to female ratio was reported.⁴⁹ Other population-based studies investigating incidence of ruptured TAA have found similar results.^{50, 51}

Intervention and admission

Variations in the intervention rates over time for both ruptured and non ruptured AAA have been reported. Two studies based on the US National Medicare Data Base revealed a decline in the incidence of hospitalizations and repair for ruptured AAA.^{3, 52} The decline in the frequency of admissions for ruptured AAA was more pronounced in men than women. One of the studies reported a decrease⁵² whereas the other reported an unchanged incidence of elective repairs.³ Data from the US Nationwide Inpatient Sample showed unchanged numbers of patients treated for both ruptured and non ruptured AAA.⁵³ Another study based on the same database showed an increase in the number of elective repairs and a decline in repairs for ruptured AAAs.⁵⁴ The contradicting results are surprising, since the studies cover approximately the same time periods.

In Scotland, an increase in the incidence of both elective and emergency admissions has been demonstrated.⁴ Data from England and Wales showed an increase in the incidence of AAA, measured by mortality rates and hospital admission rates, most pronounced in women.⁵⁵ A Swedish study reported an increase in the incidence of elective repair for men and women and an increase in the incidence of ruptured AAA in men in certain age-groups, but no such increase was found in women.⁵⁶ Studies regarding time trends are summarized in table 3.

Temporal trends could reflect implementation of screening programs, differences in national insurance policies and differences in quality of data when administrative data are used. Moreover, the majority of previous studies present data from samples of a population, persons restricted to certain ages or regions and do not analyze non ruptured and ruptured AAAs simultaneously, which makes extrapolation of the results to Swedish conditions difficult. In order to optimize health care for AAA patients it is necessary to have knowledge of temporal trends and outcome after treatment.

Table 3. Temporal trends

Author	Setting	Rupture	Non Rupture
Acosta 2006 ⁵⁶	Malmö, Sweden 2000-2004 vs. 1971-1986	↑	↑
Best 2003 ⁴	Scotland 1981-2000	↑	↑
Dillavou 2006 ⁵²	US, Medicare Inpatient Data Base 1994-2003	↓	↓
Filipovic 2005 ⁵⁵	England and Wales 1979-1999		↑
Giles 2009 ⁵⁴	US, Nationwide Inpatient Sample 1993-1998 vs 2001-2005	↓	↑
McPhee 2007 ⁵³	US, Nationwide Inpatient Sample 2001-2004	↔	↔
Mureebe 2008 ³	US, Medicare Inpatient Data Base 1995-2006	↓	↔

RISK FACTORS

Knowledge of the risk factors commonly found in patients with AAA is derived from epidemiological screening studies.^{1, 48, 57, 58} Well known, non-modifiable, risk factors are high age, male gender and a positive family history of AAA.^{1, 48, 57, 59-61} Ethnicity may play an important role as there is some evidence of higher prevalence in Caucasians compared to other ethnic groups.^{57, 61-63} Studies have reported increased familial risk for AAA and a high prevalence of AAA among

siblings of AAA patients.⁶⁴⁻⁶⁷ Previous studies regarding familial occurrence of AAA are mostly based on patient series from one or few centers and there is a lack of population-based reports covering the subject. Further studies within this field are necessary.

There is robust evidence that smoking is more common among AAA patients than persons without AAA.^{1, 32, 57, 59, 61} A history of suboptimal blood lipid profile has been reported to be associated with occurrence of AAA.^{1, 32, 57} In addition, an association with hypertension has been reported,^{32, 57, 60} but this association is difficult to assess since hypertension is often defined in studies as receiving antihypertensive medication. Many features of diabetes mellitus may influence the pathophysiology of AAA. However, diabetes is shown to be negatively associated with AAA.^{57, 61, 68, 69} The reasons for the negative association shown for AAA development remain unclear and published work in this area is limited. Studies of matrix biology have demonstrated that diabetes is associated with increased synthesis and lower degradation of matrix, in contrast to changes demonstrated in AAAs.⁷⁰ A recent study reported that hyperglycemia reduced progression of AAA induced experimentally in mice.⁷¹ Different potential effects associated with hyperinsulinaemia, hyperglycaemia and anti diabetic therapeutic agents have been discussed,⁷² but the mechanism(s) is not yet fully understood.

NATURAL HISTORY: GROWTH AND RUPTURE

Growth

It is generally assumed that the natural history of an AAA is continuous growth and eventual rupture. Growth and associated risk factors have been assessed in patients with small aneurysms or patients unfit for surgery. Annual AAA expansion rate is reported to be approximately 0.2-0.3 cm,⁷³⁻⁷⁸ but there are substantial individual variations. In the UKSAT and the ADAM trial the median annual growth rate was 0.3 cm in AAAs 4.0-5.5 cm.^{26, 79} Aneurysm with a diameter of 3.0-3.9 cm, followed outside the ADAM trial, had a median annual growth rate of 0.1 cm/year.⁸⁰

Several conditions and diseases influence AAA growth. Large initial aneurysm diameter,^{26, 73, 74, 81} smoking^{73, 76, 82} and age^{82, 83} have been reported to be risk factors for AAA growth. Presence of diabetes is associated with slower AAA growth.^{26, 73} The association between AAA growth and different manifestations of cardiovascular disease, such as suboptimal lipid profile, hypertension and low ankle/brachial pressure index are, however, less clear.^{73, 76, 84}

Female sex has been reported to be an independent risk factor for an increasing AAA growth rate^{74, 75, 78} although contradicted by others.^{73, 76, 77} In two of the studies showing no association, few women were included. Nevertheless, this is an important subject of study, particularly when taking into account the reported higher rupture risk in female AAA patients.

Statin use and angiotensin-converting enzyme inhibitor therapy have been reported to be associated with decreased AAA growth and lower rupture risk.^{78, 85} However, patients taking angiotensin-converting enzyme inhibitors were recently reported to have faster aneurysm growth, in conflict with previous results.⁸⁶ Whether or not statin or angiotensin-converting enzyme inhibitor therapy should be initiated to inhibit aneurysm expansion remain to be clarified.

Rupture

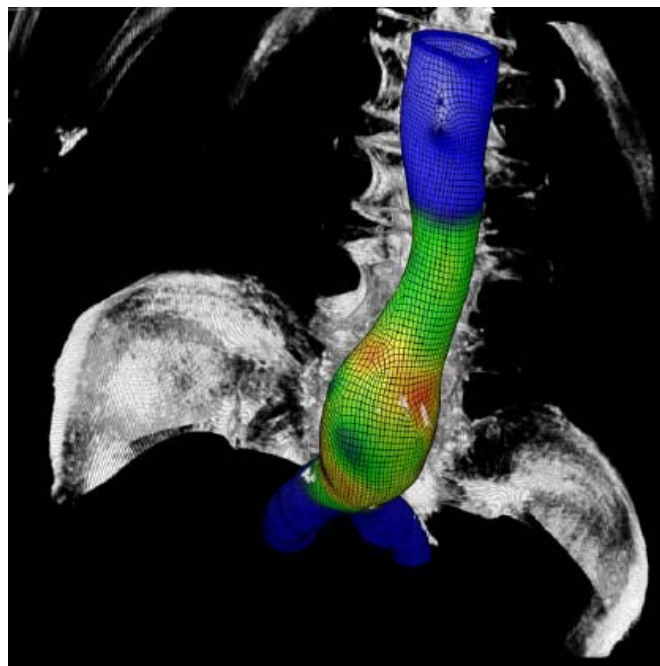
Aneurysm diameter is the currently used clinically predictor of rupture. Elective repair of AAA can prevent rupture but is associated with a non negligible risk of mortality. In the large trials comparing patients with AAAs 4.0-5.5 cm kept under surveillance with prophylactic surgery, the UKSAT and the ADAM trial, elective repair of small aneurysms was not associated with superior survival.^{26, 27} These trials have had a strong influence on management of AAA patients in clinical practice. The annual rupture rates for the surveillance groups were 0.6% in the ADAM trial and 1.0% in the UKSAT. In a study investigating the rupture rate of AAA of at least 5.5 cm in patients not planned for aortic intervention due to medical contraindications or patient refusal, the estimated yearly risk of rupture was markedly higher, 10.2% in patients with AAA ≥ 6.0 cm and 32.5% in patients with a diameter of 7.0 cm or more.⁸⁷ Due to the study design it is difficult to generalize these results to an average AAA population.

Follow up of AAA patients aims to assess the risk of rupture versus risks associated with intervention. In a follow up of the UKSAT study population and an associated study of patients monitored for aneurysm growth, including totally 2257 patients of whom 21% were women, risk factors for rupture were investigated.⁷ Low forced expiratory volume in the first second (FEV1) and current smoking were associated with the risk of rupture. A higher mean arterial pressure (MAP) increased the risk slightly, adjusted hazard ratio was 1.02 (95% Confidence Interval (CI) 1.00-1.02 per mm Hg). A threefold increased risk of rupture was recorded in women after adjustment for initial aneurysm diameter, age and body size.⁷ The risk of aneurysm rupture was four times higher in women than men in the long-term follow up of the UKSAT.²⁷ In a Finnish study of 221 patients (22% women) who died of ruptured AAA, a higher proportion of women were found among patients with ruptured AAA smaller than 5.5 cm in diameter.⁵ In a study of 476 AAA patients (21% women) considered unfit for surgery, a four time higher risk for women with aneurysms 5.0-5.9 cm compared to men was recorded.⁶ Furthermore, a study from the United Kingdom of 210 subjects (22% women) showed that women with AAA have a shorter time to rupture compared to men with the same aneurysm diameter.⁸⁸ In a report from the United States, based on the Nationwide Inpatient Sample, a higher percentage of women with AAA presented with rupture compared to men.⁵³ It is clear that women have a more unfavorable aneurysm disease compared to men. The contributing causes to the increased risk of rupture among female AAA patients are not fully understood and further studies within the area are needed.

BIOMECHANICAL ASPECTS

Aneurysm diameter allows assessment of the relative rupture risk, but not the individual risk for each patient. An aneurysm diameter of 5.5 cm is generally considered as indication for elective repair, although debated.^{26, 27} Other predictors, alone or in combination with aneurysm diameter, could probably enhance rupture risk estimations. From a biomechanical perspective, rupture of an aneurysm occurs when the mechanical stresses (force per unit area) in the aneurysm wall exceeds the strength at a single site. Reports have shown that Peak Wall Stress (PWS) predicted by a Finite Element (FE) analysis of AAA, derived from Computed Tomography (CT) images, is a better predictor of rupture than maximum AAA diameter.⁸⁹⁻⁹¹ FE analysis divides a complex geometrical structure (e.g. AAA) into a finite number of small elements. The elements are connected by nodes, and the network of elements and nodes is called a mesh. The behavior of these individual elements is expressed mathematically and combined to give the behavior of the whole geometry. Wall stress is determined by predicting movement of nodes which are influenced by the material properties of the AAA and preset boundary conditions. Aneurysms are reconstructed from contrast enhanced CT scans and analyzed with a diagnostic software (Figure 2). By adding data on wall strength, the influence of the ILT and blood pressure, Peak Wall Rupture Risk (PWRR), a parameter which includes both wall stress and strength, can be determined by FE analysis.⁹² It is likely that this method could play an important role in the future when estimating rupture risk on an individual patient basis.

Figure 2. FE-model of an AAA



TREATMENT AND OUTCOME

Elective AAA intervention to exclude the aneurysm from the circulation can prevent future rupture. There are two different methods for treatment of AAA: open repair and endovascular aneurysm repair (EVAR). The official code for classification of EVAR was introduced 1997 in Sweden and the number of patients treated for EVAR have steadily increased. According to the Swedish National Registry for Vascular Surgery (SWEDVASC), 1285 AAA interventions were performed in Sweden 2009, 49% with endovascular technique.⁹³ EVAR is associated with shorter hospital stay and intensive care unit stay. On the other hand, EVAR requires more thorough follow-up and a higher rate of re-interventions.⁹⁴ Recent studies regarding patient preference report that EVAR was preferred to open repair.^{95, 96} In summary, vascular centers must provide both open repair and EVAR and patient selection for each method must be preceded by careful consideration.

Most studies report improved postoperative survival over time after intact AAA repair.^{52, 97} Mortality after treatment for rupture are reported to remain stable over time,^{52, 97, 98} as well as to decrease.^{3, 99} The proportion of ruptured AAA treated with EVAR is increasing, there are however large variations in the utilization of EVAR.

REPAIR FOR INTACT AAA

In the Dutch Randomized Endovascular Aneurysm Management (DREAM) trial of approximately 350 patients randomized to EVAR or open AAA repair 30-day mortality was lower in the EVAR group.¹⁰⁰ In the other European trial, The United Kingdom Endovascular Aneurysm Repair Trial 1 (EVAR trial 1), including close to 1100 patients, similar results were reported.¹⁰¹ In the 2-year analyses of both these trials,^{102, 103} the early benefit associated with EVAR was already lost. Recently published long-term results showed that the early benefit was not sustained, no difference in total mortality between the two groups was found.^{104, 105} EVAR was, however, associated with higher rates of secondary interventions and was more costly.

In the Open Versus Endovascular Repair (OVER) trial from the United States, including approximately 900 AAA patients randomized to EVAR or open repair, perioperative mortality was lower for EVAR compared to open repair¹⁰⁶, in agreement with the European trials. Follow up of the OVER trial, reporting 2 years on 80% of randomized patients, failed to show a difference in mortality between EVAR and open repair. There was no increase in mid-term mortality after EVAR compared to open repair in the OVER trial, which differs from the results in the DREAM trial and the EVAR trial 1.

The proportion of female participants in these trials is low, less than 1% in the OVER trial, 9% in the EVAR-1 trial and 8% in the DREAM trial. In a cohort of AAA patients the expected proportion of women would be approximately 15-25%. It is

therefore worth noting that the proportion of women in these randomized controlled studies is lower than the proportion of women among AAA patients overall. A contributing explanation could be that women are usually described as having a more complex anatomy than men, especially in the proximal neck¹⁰⁷⁻¹⁰⁹ which could make them less suitable as candidates for EVAR and therefore not possible to randomize. Gender distribution in the source populations for the study samples could obviously also contribute to this. Characteristics and results of the three randomized trials are summarized in table 4.

Table 4. Randomized controlled trials comparing EVAR and open AAA repair

	Trial		
	EVAR-1	DREAM	OVER
Randomized patients (N)	1252	351	881
Women (N, %)	117 (9)	29 (8)	5 (<1)
Median follow up time (years)	6.0	6.4	1.8
30 day mortality or inpatient mortality	Lower in EVAR group (1.8% vs. 4.3%)	Lower in EVAR group (1.2% vs. 4.6%)	Lower in EVAR group (0.5% vs. 3.0%)
All-cause long term mortality	No difference	No difference	No difference
Aneurysm related mortality	No difference	No difference	No difference
Comments	Early benefit in aneurysm-related mortality in the EVAR group.	Early benefit in aneurysm-related mortality in the EVAR group	No difference in secondary therapeutic procedures.
	Higher rates of reinterventions in EVAR group	Higher rates of reinterventions in EVAR group	No increase in mid-term mortality after EVAR was observed, differ from the results in the other 2 trials.

REPAIR FOR RUPTURED AAA

Rupture of an AAA is fatal in the majority of cases and is an important cause of sudden death. In Sweden 306 interventions (69 EVAR) for rupture was performed in 2009 according to SWEDVASC.⁹³ The accurate number of ruptures is obviously higher due to patients with ruptured AAA who are being declared unfit for intervention, patients with ruptured AAA who die before reaching hospital and

due to misclassifications of sudden deaths. The autopsy frequency in Sweden was approximately 14% in 2006 and even lower in persons older than 75 years.¹¹⁰ The mortality associated with intervention for ruptured AAA in patients reaching hospital and treated is approximately 40%.⁸ The overall mortality associated with rupture is even higher. In a study from Malmö, Sweden, early mortality in ruptured AAA, defined as death outside hospital or during the hospitalization was 74%.⁵⁶

It has been reported that women are less likely than men to be offered surgical repair of ruptured AAA.^{53, 111-114} Theoretically the higher mean age in female AAA patients could be the explanation, but the gender difference remains after adjustment for age and comorbidity in multivariate regression models. Thus, the reasons remain to be investigated.

OUTCOME: GENDER DIFFERENCES

Outcome studies on gender differences after AAA surgery have reported varying results. It has been shown that women have worse short and long term outcome than men, both after elective and acute AAA repair. The difference remained even after adjustment for the higher age in women.^{53, 112, 114-117} Other reports have failed to show a gender difference in mortality.^{98, 111, 118} Long term survival can also be estimated as relative mortality or Standardized Mortality Ratio (SMR), which implies a comparison with a matched population. Persons surviving AAA intervention do not have similar survival rates as the general population. This patient group have an increased risk of premature death compared with the age matched population.^{8, 9, 119} The SMR is also markedly higher for AAA patients treated at a younger age compared to older persons.⁸

Interestingly, women treated for AAA have higher relative long term mortality than men.^{8, 9, 120} In a previous study from our group SMR for women treated for AAA was 2.26 compared to 1.63 for men ($p < 0.0001$ for gender difference).⁸ This emphasizes that women with AAA may have the same high risk of premature death as men with AAA, but compared to other women in the population their risk is considerably increased.

A different disease profile for men and women treated for AAA as reflected by causes of death has also been reported.⁸ Women treated for AAA more often died due to aneurysm-related causes, possibly rupture of a TAA. The prevalence of TAA in patients with AAA is, however, unknown. Previous studies within this field have not addressed the prevalence of TAA in a general population of untreated AAA patients. Considering the reported association between gender and increased risk of aneurysm-related death after AAA intervention, the occurrence of concurrent TAA and AAA ought to be investigated.

GENDER: DIFFERENCES BETWEEN MEN AND WOMEN WITH AAA, THE ROLE OF ESTROGEN

There are several gender differences in AAA patients besides the difference in prevalence. Men are younger at the time of diagnosis and intervention, have a lower rupture risk, possibly have better outcome and are treated to a higher extent compared to women. Despite attempts to clarify these differences several questions remain to be answered. The protective effect of endogenous estrogen on the development of the disease will probably continue to be the most widespread explanation for the gender difference in age until other mechanisms have been described. Postmenopausal hormone therapy does not prevent women from cardiovascular disease.¹²¹ It has been demonstrated that estrogens affects the aortic collagen to elastin ratio in rats.¹²² Ailawadi et al exposed rats to elastase perfusion of the infrarenal aorta and made comparisons between female and male rats. Less destruction of the media in the vessel wall, less macrophage infiltration and lower levels of MMP-9 were found in female rats.¹²³ The aneurysm protection that female aortas exhibited in situ diminished after their transplantation into male rats, whereas female aortas transplanted into other female rats maintained their aneurysm protection.¹²³ In summary, further attention should be paid to the possible influence of estrogen on aneurysm development and growth.

AIMS OF THE THESIS

- Study I: To investigate temporal trends in number of procedures and outcome after intervention for ruptured and non ruptured AAA with special focus on gender differences.
- Study II: To clarify the risk of developing an AAA for first degree relatives of patients with the disease.
- Study III: To elucidate the prevalence of TAA in AAA patients and to investigate possible gender differences.
- Study IV: To investigate the increased rupture risk in women with AAA compared to men from a biomechanical perspective using a state-of-the-art biomechanical FE model.

MATERIAL AND METHODS

REGISTERS

National Registration Number

All Swedish citizens have a unique 12-digit personal national registration number that facilitates identification on a patient-specific level in national registers and enables linkages between different registers.

The Swedish Inpatient Register

The Swedish Inpatient Register or National Hospital Discharge Register (*Sw: Patientregistret or Slutenvårdregistret*) is managed by the Swedish National Board of Health and Welfare (NBHW) and covers all information regarding public inpatient care. It was established in 1964 in order to register individual hospital discharges and has complete nation-wide coverage since 1987.¹²⁴ The discharge codes are classified according to the *International Classifications of Diseases (ICD)*, ICD 7 until 1968, ICD 8 during 1969-1986, ICD 9 during 1987-1996 and from 1997 and onwards ICD 10. The register also contains procedure codes according to the *Classification of Surgical Procedures*. Each in-hospital care episode corresponds to one record in the register and contains the personal identification number, hospital, dates of admission and discharge and up to 8 discharge diagnoses of which one is the principal. In 2006, 99% of all care episodes were registered, the loss of 1% was mainly found in the psychiatric care.¹²⁴ The public health care in Sweden is accessible for all residents. No patients are treated for AAA in the private sector.

The Cause of Death Register

The Cause of Death Register (*Sw: Dödsorsaksregistret*) is managed by the Centre for Epidemiology at the NBHW. The register records data for cause and time of death for all deceased Swedish residents. Stillborn infants, persons who die during a temporary stay in Sweden or asylum seeking persons are not included in the register. Completeness is estimated to exceed 99% and data is updated yearly.¹²⁵ The causes of death are classified according to the ICD system.

The Multi-generation Register

The Multi-generation Register (*Sw: Flergenerationsregistret*) is maintained by Statistics Sweden and consists of Swedish residents born after 1931, called index persons. The register contains linkages between the index persons and their children, siblings and parents. Regarding the relatives there is no age limitation.

In 2005 the coverage was 85% for known mothers and 82% for known fathers. For index persons born in Sweden the corresponding figures were 97% and 95%. The number of index persons is approximately 9 million.¹²⁶

Register of Total Population

The Register of Total Population (*Sw: Registret över totalbefolkning*) is managed by Statistic Sweden and contains data of Swedish census since 1968.

STUDY I

Design and study population

Study I is a population-based cohort study, covering the entire Swedish population. Data for all individuals treated for non ruptured or ruptured AAA in Sweden from 1990 to 2005 were obtained from the Inpatient Register. The extraction of data was based on the procedural codes for AAA, according to the *Classification of Surgical Procedures* by the NBHW (edition 5, 6, and 7) and the diagnostic codes for AAA classified by clinical modifications 9 and 10 of the ICD. The number of persons treated, age at treatment, sex, and procedural codes were analyzed on a patient-specific level. Information about time for death and cause was extracted from the Cause of Death Register.

Statistical analysis

Crude comparisons of proportions were performed by χ^2 tests. Poisson regression was used to analyze trends of surgical interventions, where population figures specific for age, sex, and calendar year were used as the denominator (i.e., as an offset). Trends in age at surgery were analyzed by linear regression. A logistic regression model was applied to derive odds ratios (ORs) and corresponding 95% confidence intervals (CIs) for mortality in different time windows up to 1 year, considering sex, rupture vs. non rupture, 10-year age groups, and calendar year.

STUDY II

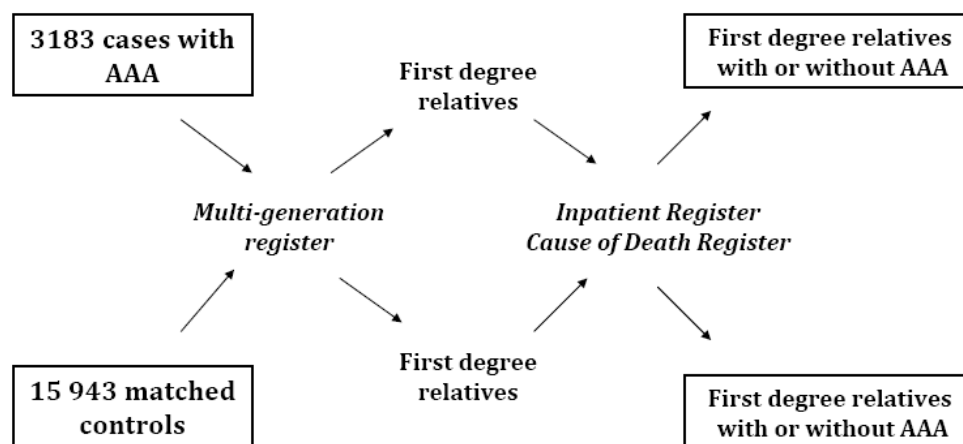
Design and study population

Study II is a population-based case-control study covering the entire Swedish population. Cases (n=3183) were defined as all persons found in the Inpatient Register with a first admission under the diagnosis of AAA (I71.3, I71.4, I71.8, or I71.9) between 2001 and 2005, and all persons found in the Cause of Death Register, deceased during the same period with the corresponding underlying cause of death who were not found in the hospital register. A random selection of 15943 age, gender, calendar year, and region matched controls were identified and data for these persons were extracted from the Register of Total Population.

Exposure

The exposure, i.e. family history of AAA, was obtained by identifying first degree relatives (FDR) of cases and controls in the Multi-generation Register. Family history of AAA was assessed by linking the identified relatives to the Hospital Discharge Register and Cause of Death Register, thereby all FDRs of the cases and the controls affected by AAA were identified. Comorbidity for cases and controls was assessed by the prevalence of admissions with selected diagnoses 5 years prior to the diagnosis date for the case and the corresponding period for the matched controls. The study design is summarized in figure 3.

Figure 3. Design of study II.



Statistical analysis

Crude comparisons of proportions were performed by χ^2 -tests. Conditional logistic regression was applied to calculate ORs and corresponding 95% CIs for the risk of AAA in relation to positive family history of AAA. Risks associated with family history were assessed with respect to the number and the gender of affected FDRs. Potential effect modification of age, gender and diagnosis (rupture vs. non rupture) were investigated in stratified analysis and tested by likelihood ratio tests. Risks in relation to family history were adjusted for presence of comorbidity. We also performed an interaction analysis of the effect of family history among cases and controls with and without any comorbidity, which was tested by a likelihood ratio test.

STUDY III

Design and study population

Study III can be referred to as a cross sectional study investigating the prevalence of TAA in a population of AAA patients. Consecutive AAA patients (aortic diameter ≥ 30 mm) attending the out-patient clinic at Karolinska University Hospital, Stockholm, Sweden, from January 1, 2004, to December 31, 2008 were identified (n=1055) in a hospital register of the out patient clinic. The inclusion criteria for the identified patients were abdominal and thoracic CT scan. Patients were excluded if they were previously diagnosed with any pathology in the thoracic aorta to avoid a “diagnostic bias”. Patients with a known pathology in the thoracic aorta have a high probability of being examined with a thoracic CT. Furthermore, patients were excluded if the CT was performed in connection with rupture, if they had undergone a previous aortic intervention, if they suffered from a genetic disease of the connective tissue (e.g. Marfan’s Syndrome) or if they had undergone separate CTs of abdomen and thorax with a time interval exceeding 6 months. In total, these criteria identified 354 patients, representing 33.6% of the 1055 patients with AAA. Inclusion and exclusion is described in figure 4 Height, weight, smoking and comorbid conditions were recorded from hospital charts.

Figure 4. Flow chart of included patients

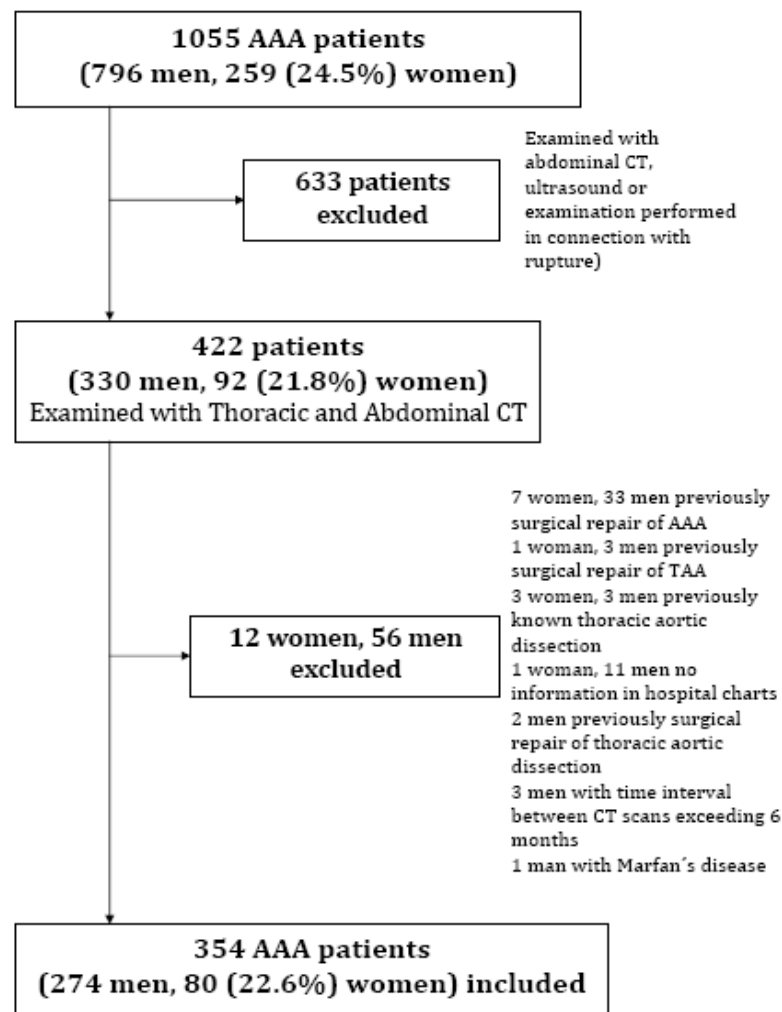


Image analysis

The available CT examinations were performed on a 4-, 16- or 64-slice multidetector CT scanner performed during arterial phase after intravenous contrast injection. 36 CTs were performed without contrast. One external radiologist reviewed all CT scans. The interobserver variability of the measurements was tested in 15 cases by an experienced radiologist, blinded to the initial results. The Standard Deviations (SD) of the difference was 1.14 mm for interobserver variability. The SD for intraobserver variability, also tested in 15 cases, was 1.16 mm. Image analysis was performed on a Picture Archiving and Communication System (Sectra). Available CT scans of aorta had slice thicknesses varying from 0.6 to 5 mm between the different examinations. In contrast enhanced scans the diameters were measured from the outer contours of the enhanced vessel, and in scans performed without contrast between medium points of the vessel wall (n=36). The maximum diameter of ascending aorta, descending aorta and abdominal aorta were measured in each case.

Comparisons with recently published diameters in an average elderly Swedish population, and suggested cut off values based on diameters exceeding 2 SDs were used to define a TAA.²⁵ CT and Magnetic Resonance Imaging (MRI) have been compared previously regarding evaluation of the aorta and were found to be equal.¹²⁷

Statistical analysis

Crude comparisons of proportions were performed by χ^2 tests. Continuous variables were evaluated with Mann-Whitney Test for non parametric variables (age and aortic diameters) and t-test for parametric variables (height and weight). The presence of TAA was estimated by logistic regression and ORs with corresponding 95% CIs. Adjustments for possible confounding were made in a multivariable logistic regression model. An interaction analysis of gender and all the separate comorbidities was performed and tested by a likelihood ratio test.

STUDY IV**Design and study population**

Study IV is a pilot study using a biomechanical FE model to investigate the increased rupture risk in women with AAA compared to men. 15 men and 15 women with known infrarenal AAA followed at the in-patient clinic at Karolinska University Hospital, Stockholm, Sweden were included. Inclusion criteria were an AAA diameter of 4-6 cm and having undergone contrast enhanced CT. All patients had a CT as part of their regular evaluation of AAA.

Finite Element Analysis

FE analysis divides a complex geometrical structure (e.g. AAA) into a finite number of small elements. The elements are connected by nodes, and the network of elements and nodes is called a mesh. The behavior of these individual elements

is expressed mathematically and combined to give the behavior of the whole geometry. Wall stress is determined by predicting movement of nodes which are influenced by the material properties of the AAA and preset boundary conditions.

Aneurysms were reconstructed from contrast enhanced CT scans and analyzed with the diagnostic software A4research (VASCOPS GmbH, Graz, Austria), details are given elsewhere.¹²⁸ PWS and PWRR were calculated from patient specific FE models, where non-linear isotropic constitutive descriptions of the wall¹²⁹ and ILT¹³⁰ as proposed previously were used. Specifically the weakening and thinning effect of the ILT on the wall were considered. Finally, the structural analysis applies mean arterial pressure at the lumen and fixes the aneurysm at the renal arteries and the aortic bifurcation; no contact with surrounding organs was considered.

Gender aspects on the model

Comparing patients with identical AAAs, women is reported to have an aneurysm wall that is globally weaker compared to a men.¹³¹ The software in the present study takes this gender difference into account. A FE analysis is based on both geometrical and biomechanical properties of the aneurysm. To investigate this interrelation deeper we additionally therefore performed a FE analysis where female patients were analyzed with “male tissue properties”, i.e. comparing males and females with the same tissue properties and not taking into account that women have a globally weaker AAA. This especially designed group was named “gender neutral group” and like all geometrical properties, the ILT will of course not be affected by the transformation.

A general comparison of “small” (diameter 40-50 mm) versus “large” (diameter 51-60 mm) aneurysms was also performed in order to test the model in this respect. The aorta was segmented between the renal arteries and the aortic bifurcation and reconstructed in three dimensions, hence all geometrical (aneurysm diameter and ILT volume) and mechanical (PWS and PWRR) determinants were derived.

Statistical analyses

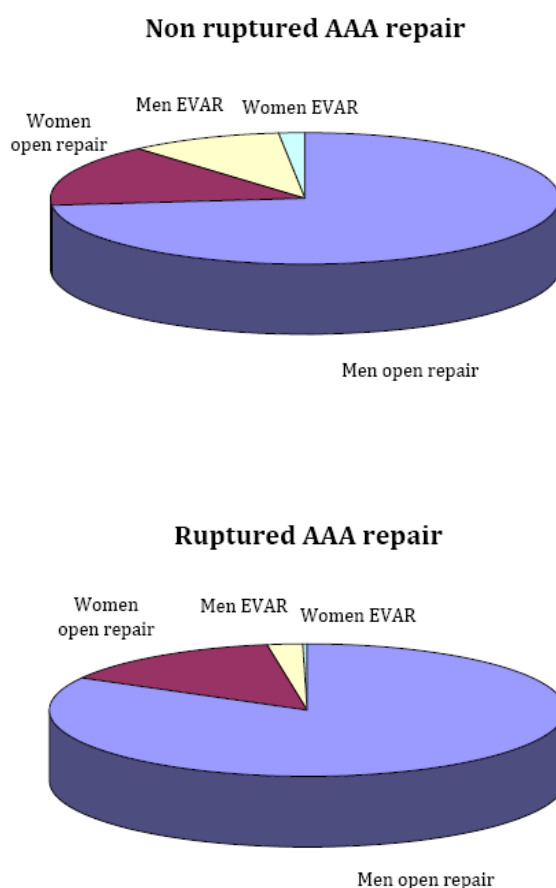
Gender comparisons and comparisons between small and large aneurysms were performed by independent t-test for all variables, except Mean Arterial Pressure (MAP) which not was normally distributed and thus analyzed with Mann-Whitney test.

RESULTS

STUDY I

The aim of study I was to investigate recent temporal trends and outcome in Sweden for procedures performed for AAA, with special emphasis on gender differences. The study includes all patients (n=14369) treated with open repair or EVAR for non ruptured or ruptured AAA from 1990 to 2005. More patients (65.4%) were treated for non ruptured compared to ruptured AAA. Overall, the majority of the patients (83.8%) were male. The gender distribution, aneurysm type and intervention are given in figure 5.

Figure 5. Non ruptured and ruptured AAA repair in Sweden 1990-2005



Non ruptured AAA

The number of patients treated for non ruptured AAA was 9401 (16.9% women). Figure 5. From 2002 to 2005, this represents an overall intervention rate of 30.6 per 100000 inhabitants for non ruptured AAA in persons aged >60 years. There was no significant increase in the proportion of female patients treated for non ruptured AAA during the observation period, 16.4% in 1990 and 18.2% in 2005 ($p=0.17$). In the Poisson regression model, a 4% relative annual increase in the intervention rate for non ruptured AAA was recorded for women ($p<0.0001$), the corresponding figure for men was 2% ($p<0.0001$).

Crude postoperative mortality ≤ 30 days for non ruptured AAA was lower in men compared to women (4.9% vs. 5.7%). However, this gender difference disappeared after adjustment for age, EVAR, and calendar year in the multivariate logistic regression model. The most common cause of death at 30 days was cardiovascular disease (women, 88%; men, 90%; $p=0.57$).

Ruptured AAA

Of 4968 patients treated for ruptured AAA, 14.8% were women. Figure 5. There was no significant increase in the proportion of women treated for ruptured AAA, 15.8% in 1990 and 18.5% in 2005, although a trend towards an increase in the proportion of women was observed ($p=0.06$). Between 2002 and 2005 a mean of 15.0 interventions per 100,000 inhabitants aged >60 years were performed. In the Poisson regression model no significant annual relative increase in interventions for ruptured AAA was observed during the observation period, neither for women nor men.

35.1% of all men treated for AAA in Sweden 1990-2005 were treated for ruptured AAA. Among women the corresponding figure was 31.7%. This gender difference was statistically significant ($p<0.001$).

Overall postoperative mortality within 30 days after intervention for ruptured AAA was 37.6%. Women treated for ruptured AAA had a higher crude 30-day mortality compared with men (41.9% vs. 36.8%). Similar to non ruptured AAA, this gender difference disappeared after adjustments in the logistic regression model. Patients treated for rupture continued to have high crude mortality rate related to surgery during the first 6 months. The most common cause of death at 30 days was cardiovascular disease, no gender differences were detected.

STUDY II

The aim of study II was to investigate the risk of AAA associated with a positive family history of AAA. Cases with AAA ($n=3183$) were included, identified from the Cause of Death Register ($n=479$) and the Inpatient Register ($n=2704$). Age, gender, calendar year, and region matched controls ($n=15943$) were identified in the Register of Total Population and included in the study. Of the cases and

controls, 16.8%, were women. A positive family history of AAA was more common among cases than controls (8.4 vs. 4.6%, $p<0.0001$). Characteristics of cases and controls are given in table 5. The prevalence of comorbidities was more common among cases than controls (30.4% vs. 11.1%, $p<0.0001$). The proportion of cases with a positive family history was similar in patients with ruptured and non-ruptured AAA.

Table 5. Characteristics of cases and controls

Characteristics	Cases (n=3183) No (%)	Controls (n=15943) No (%)	p-value
Gender			
Female	535 (16.8)	2679 (16.8)	0.9951
Family history of AAA			
Yes	268 (8.4)	743 (4.6)	<0.0001
Diagnosis			
Rupture	840		
With family history	61 (7.3)		
Non rupture	2342		
With family history	207 (8.8)		

The overall relative risk of AAA associated with a positive family history of AAA compared to no family history was approximately doubled. The relative risks remained unchanged after adjustment for comorbidities. Table 6. If more than one first-degree relative had AAA the risk increased further.

Table 6. Relative risk of AAA

	Odds Ratio (95% CI)	
	Unadjusted	Adjusted for comorbidity
Family history		
No	1.0 (ref)	1.0 (ref)
Yes	1.9 (1.6-2.2)	1.9 (1.6-2.2)

We also performed a logistic regression analysis stratified for absence or presence of comorbidities. The relative risk of AAA associated with family history was similar ($p=0.29$) for persons without comorbidities (OR 1.7) compared to those with comorbidities (OR 2.4).

In a subgroup analysis, no differences were found between different age groups ($p=0.75$) or between patients treated for ruptured and non-ruptured AAA ($p=0.42$) in the relative risk of AAA associated with a positive family history. No gender difference in the relative risk of AAA associated with family history could

be demonstrated ($p=0.22$), i.e., the relative risk of AAA was not dependent on the gender of the index person. Furthermore, there was no significant difference in the relative risk of AAA when having a female compared to a male first degree relative with AAA. Table 7. There was, however, a tendency toward an increased relative risk when having a male FDR compared to a female FDR ($p=0.07$).

Table 7. Relative risk of AAA given gender of the index person and the first degree relative (ref: no family history)

	Odds ratio (95% CI)	
	Female relative	Male relative
Male index person	1.6 (1.3-2.0)	2.1 (1.7-2.5)
Female index person	1.8 (1.1-2.9)	3.1 (1.9-5.0)

STUDY III

The aim of study III was to investigate the prevalence of TAA in patients with AAA. 354 patients, of whom 80 (23%) were women, met the inclusion criteria. There were no differences in comorbidities between men and women except for a higher proportion of female smokers (49% vs. 31%, $p=0.003$). Women were older than men. A significant difference in aortic diameter in absolute terms between women and men was found in the ascending, but neither in the descending nor the abdominal aorta. Age and diameters are given in table 8.

Table 8. Patient characteristics

	Men (n=274) Median (range)	Women (n=80) Median (range)	p-value
Age (years)	74.0 (49-91)	75.5 (49-88)	0.021
Diameter (mm)			
Abdominal aorta	56.0 (31.0-129.2)	53.0 (32.3-100.2)	0.054
Ascending aorta	36.6 (26.8-58.3)	34.3 (28.6-61.9)	0.003
Descending aorta	33.1 (21.5-63.9)	31.8 (23.3-73.0)	0.220

Further analysis used gender specific criteria for TAA.²⁵ Approximately one fourth, 100 (28%) of the 354 patients with an AAA, had a concurrent TAA. Based on gender specific aneurysm criteria, 48% of the women had a TAA compared to 23% of the men ($p<0.0001$). See table 9 for details.

Table 9. Number of AAA patients with concurrent TAA using gender specific criteria

Aneurysm	Men	Women	p-value
	No (%)	No (%)	
Ascendens	6 (2.2)	6 (7.5)	0.021
Descendens	57 (20.8)	37 (46.3)	<0.0001
Asendens and/or Descendens	62 (22.6)	38 (47.5)	<0.0001

(1 male patient, and 5 female patients suffered from both ascending and descending aneurysms).

When similar criteria were applied for men and women, descending aortic aneurysms were present in 78 patients (21 women and 57 men), representing 22% of the patients.

Women with AAA had an approximately three times higher risk of concurrent TAA than men (OR 3.09, 95% CI 1.84-5.22) in a univariate logistic regression model, when using gender specific criteria. In the multivariate model (adjusted for smoking, chronic obstructive pulmonary disease, heart disease, hypertension, diabetes mellitus and age) there was still an approximately 3-fold increased risk for women (OR 2.80, 95% CI 1.61-4.89). Analysis of possible effect modification did not reveal any interactions between gender and presence of comorbidity.

STUDY IV

The aim of study IV was to investigate the increased rupture risk in women with AAA compared to men from a biomechanical perspective. 15 men and 15 women (AAA 4-6 cm) were included. There were no significant gender differences in mean age (73 vs 71 years, $p=0.42$), mean aneurysm diameter (49.7 vs. 50.1 mm, $p=0.83$) or median MAP (100 vs. 102, $p=0.21$).

PWS was similar for women and men; 184 vs. 198 kPa ($p=0.42$). Mean PWRR was 0.54 for women and 0.43 for men, $p=0.06$. There were no gender difference in mean ILT volume between women and men. Table 10.

Table 10. Peak Wall Stress (PWS), Peak Wall Rupture Risk (PWRR) and Intraluminal Thrombus (ILT) volume in men and women

Biomechanical properties	Gender		p-value
	Mean (range)	Mean (range)	
	Men	Women	
PWS (kPa, mean)	198 (111-266)	184 (120-282)	0.42
PWRR (mean)	0.43 (0.24-0.66)	0.54 (0.28-0.85)	0.06
ILT (mm ³ , mean)	45008 (2371-114679)	42070 (714-83361)	0.81

Patients with large aneurysms (diameter 51-60 mm) had higher mean PWS (211 vs. 168 kPa, $p=0.01$) and mean PWRR (0.55 vs. 0.41, $p=0.01$) compared to patients with small aneurysms (40-50mm). The gender distribution among patients with large compared to patients with small aneurysms was similar; 7 women and 7 men had a diameter of 40-50 mm and 8 women and 8 men had a diameter of 51-60 mm.

In the FE analysis of the “gender neutral group”, i.e. where female patients received the same aneurysm wall tissue properties as males, no difference in mean PWRR between women and men was found (0.38 vs. 0.43, $p=0.24$). The mean PWS in this analysis was also similar; 179 for women and 198 kPa for men ($p=0.28$).

DISCUSSION

METHODOLOGICAL CONSIDERATIONS

Epidemiology, "the study of what is upon the people", is derived from the Greek terms *epi* = upon, among; *demos* = people, district; *logos* = study. Epidemiology is traditionally defined as the study of disease occurrence and considered to be the fundamental of public health science.

Study design

Epidemiological studies can be divided into two types; *experimental* and *observational*. The term experiment usually implies that the investigator manipulates the exposure assigned to participants in the study.¹³² Cohort, case-control, cross-sectional and ecological studies can all be named *observational*. Randomized control trials are generally considered to generate more reliable results than observational studies and are considered to be the "gold standard". However, observational studies have advantages including greater timelines and a broader range of patients.¹³³ Experimental studies can be unfeasible when investigating harmful exposures leading to ethical considerations or too costly and time consuming to perform in relation to the expected scientific value of the study.

Study I in the present thesis is a population-based cohort study, covering the entire Swedish population. All patients treated for AAA in Sweden 1990-2005 were included; temporal trends in treated patients and mortality after intervention were investigated. Study II is a population-based case-control study, investigating the exposure of a positive family history of AAA on the risk for AAA. Study III can be referred to as a cross-sectional study investigating the prevalence of TAA in a population of AAA patients. Study IV is a pilot study using a biomechanical FE model to investigate the increased rupture risk in women with AAA compared to men.

Validity in estimation

Findings in an epidemiological study may reflect the true relationship between exposure and outcome but the possibility of an alternative explanation; *bias*, *confounding* or *chance* should be considered. Errors in estimation refer to systematic or random errors. The main obstacles for high validity in a study are systematic errors, often called bias, and confounding which also could be referred to as a systematic error. Systematic errors is the opposite of validity the opposite of random errors is precision.¹³²

Generalizability

Internal validity describes the validity of the inferences drawn to the members of the source population. The presence of bias and confounding in a study could result in low internal validity. Internal validity is a prerequisite for *external validity*, or generalizability, which refers to the validity of the inferences drawn to people outside the source population.

Study II

Due to the design of the Multi Generation Register, the results in study II are based on AAA cases 73 years and younger. It is possible that “inherited” AAAs debut in patients at a younger age compared to AAAs without positive family history. However, we could not demonstrate any effect modification of age. No pattern towards increased relative risk for younger persons was observed.

Study III

Some remarks need to be made regarding external validity in study III. At the time of the CT scans, no general guidelines regarding radiological examination of the thoracic aorta in patients with AAA were applied in clinical practice at the Karolinska University Hospital. After hospital chart review it became obvious, although not possible to show in context of a statistical analysis, that no systematic patterns could be recognized in the selection of AAA patients examined with thoracic CT. If one assumes that not a single TAA is found among the excluded 633 AAA patients due to examination with only abdominal CT, ultrasound or CT performed in connection with rupture (Figure 4), the prevalence of AAA is still approximately 10% (100 TAA among 987 patients). This situation is, however, highly unlikely. An underestimation of the prevalence of TAA in AAA patients is more probable since patients with known TAA were excluded from the study. In summary, despite possible issues with generalizability, the results indicate that radiological examination of the thoracic aorta should be considered in AAA patients.

The proportion of female patients (23%) in the study is similar to the previously reported fraction of female patients in prevalence studies and surgical series. The distribution of women included in the study is equal to the excluded group of patients from our out-patient clinic (23% vs. 26%). The higher mean age for women also comprehends to reported differences in mean age between genders. Thus, included patients in study III most likely reflect a general AAA population attending an out-patient clinic.

Bias

Bias may be defined as any systematic error that results in an incorrect estimate of the association between exposure and outcome.¹³⁴ Selection bias refers to errors in the process of identifying the study population. Information bias or misclassification refers to systematic errors in estimating an effect caused by measurement errors. Non differential misclassification of exposure occurs when

the proportion of subjects misclassified does not depend on the disease status, and vice versa regarding misclassification of disease. Differential misclassification of exposure occurs if the misclassification of exposure is different for those with and without disease, and the opposite regarding misclassification of disease.¹³²

Selection bias

Study I and II

Public health care in Sweden is accessible to all residents. No patients are treated for AAA in the private sector. In a validation of the Swedish Inpatient Register performed by the NBHW in 1990, errors were divided into errors in transmission of diagnostic codes from charts to register (*i*), errors in choosing correct code compared to diagnosis reported in hospital chart (*ii*) and errors in choosing the correct diagnosis (*iii*).¹²⁴ AAA is a condition which is rarely misclassified. Few ICD-codes and surgical procedure codes correspond to AAA. Altogether, this would minimize the risk of errors in choosing the accurate code (*ii*) and accurate diagnosis (*iii*). Errors in the transmission of the diagnostic codes from the charts to the register (*i*) would thereby be the biggest concern regarding AAA. This type of error has been shown to be very low (0.3%) in the validation done by the National Board of Health and Welfare. In 1993 0.1% of the surgical procedure codes were missing or not valid,¹³⁵ it is not likely that this number has increased the last years.

In order to be included in study I, patients had to have both the accurate diagnostic code and the accurate surgical procedure code corresponding to AAA. It is possible that some persons treated for AAA are missing in study I due to these strict inclusion criteria. On the contrary, it is highly unlikely that a person designated as having undergone AAA intervention in fact has not. This small possible loss in sensitivity does not affect the principal outcome of interest; temporal trends and mortality after intervention. A minimal underestimation of the incidence is however not completely ruled out. In a report based on data from SWEDVASC 1994-2005, 10691 patients were included.¹³⁶ During the same time period 11280 patients were included in study I, thus a difference of 589 patients. Despite fewer AAA cases, crude mortality rates were lower in the SWEDVASC report.

Study II

Some comments are necessary regarding possible more frequent AAA screening among family members of persons with known AAA. Knowing that you have a family member with AAA could lead to a higher probability of investigation for AAA, leading to potential selection bias. However, the cases were extracted from the Inpatient Register at the time of their first admission for AAA between 2001 and 2005, and all persons deceased during the same period with the corresponding underlying cause of death that was not found in the hospital register. This design likely minimizes bias due to possible opportunistic family screening. Moreover there were no difference in the relative risk associated with

a positive family history between cases diagnosed with ruptured and cases diagnosed with non ruptured AAA.

Misclassification

Study II

The Swedish Inpatient Register has complete nation-wide coverage since 1987.¹²⁴ Before 1987 different counties in Sweden were represented at various levels of coverage in the Inpatient Register. In study II, cases and controls were matched on gender, age and region. The region matching facilitates equal probabilities for cases and controls to have a recorded family history, minimizing possible non differential misclassification of exposure. Unknown relatives, unreported ruptured AAA due to inaccurately assigned causes of death and low autopsy rates¹¹⁰ is possible, resulting preferentially in misclassification of exposure. These misclassifications are, however, likely to lead to a dilution of the relative risk of AAA associated with a positive family history.

Confounding

Confounding may be considered as confusion of effects.¹³² A confounder is associated with the exposure and influences the risk of developing the outcome, but is not an intermediate factor in the causal pathway. Confounding should not be confused with effect modification, where measures of effect vary over different values of the same variable.¹³⁷ Effect modification should be reported and described, whereas confounding can be controlled for in different ways in the study design and analysis of data.

Study I, II and III

In study I, II and III confounding was addressed with multiple regression models. When selecting predictors to include in the regression models, we included well-established or probable causal factors and factors considered as clinically relevant without regard to the strength or statistical significance of their association with the predictor of primary interest and outcome. Even though confounding was rather well accounted for, residual confounding can never completely be ruled out.

Information of smoking status is not available in the Swedish Inpatient Register and therefore not included in the regression model in study II. However, adjustments for other comorbid conditions were made.

Random errors

Random errors remain to be addressed after the systematic errors. Precision is statistically reflected by the p-value and the confidence interval. The p-value is a function of the strength of the association of interest and the size of the sample. The p-value should be used with caution; a non significant p-value is not equivalent to a true null hypothesis. The confidence interval mirrors the range, with a certain degree of uncertainty, within the true magnitude of the effect. The

probability of rejecting a false test hypothesis is called the power of the study. Type I error refers to the situation where the null hypothesis is incorrectly rejected, which often is the issue in multiple testing. Type II errors occur when there is a true effect but the study fails to show it, often the result of a small sample size.

Study I, II and IV

The large size of study I and II provides a good basis to minimize the likelihood of random errors. It is unlikely that the results are due to chance. A type II error could possibly be seen in study IV, due to small sample sizes.

FINDINGS AND IMPLEMENTATIONS

Temporal trends

In Sweden, there has been an annual increase in persons treated for non ruptured AAA, but no increase was recorded for ruptured AAA (study I). A higher detection rate due to an increasing number of radiologic investigations, as well as an improved awareness of the disease could contribute to this finding. The rise in procedures performed for non ruptured AAA could also reflect an increase in the prevalence of AAA.^{55, 56, 138} Screening for AAA had not yet started in Sweden during the study period.

Evaluations of time trends are difficult and recent studies have not been consistent. Differences in study designs, inclusion criteria, implementation of screening programs and health care policies could obstruct comparisons. In contrast to most reports from the US,^{3, 52, 53} the majority of European reports^{4, 55, 56, 139} correspond to our findings in study I, with a general increase in elective repairs. In the report from Mureebe et al³ based on the US Medicare inpatient database, approximately 83 per 100000 Medicare beneficiaries underwent repair for non ruptured AAA yearly. In study I we demonstrated that approximately 31 per 100000 inhabitants aged >60 years were treated for non ruptured AAA. One could speculate that the higher number of patients treated in the US reflects a situation where the number of persons treated represents the actual number of persons eligible for elective AAA repair. The lower incidence rates in Europe could indicate that the intervention rates will continue to increase even more in the future.

Knowledge of temporal trends regarding intervention and postoperative results for men and women with AAA is important, especially when future health care strategies are discussed. AAA screening programs of 65 year old men have started in several counties in Sweden. The prevalence is lower than expected according to preliminary reports. The expected life-span is steadily increasing in Sweden.¹⁴⁰ The increasing mean age in study I could reflect this and a more generous attitude towards treating elderly patients. With the increasing life expectancy and

implementation of screening, intervention rates for elective AAA repair will probably continue to increase in Sweden.

To interpret the unchanged or falling rates of interventions for ruptured AAA in contrast to the increase of elective procedures, a reflection of an “optimal” detection rate of elective repair can be tempting. One must however consider that the estimated number of persons in the Swedish population affected by AAA, based on prevalence figures,^{1, 2, 57} ought to be substantially higher than the number of persons currently diagnosed or treated for AAA. One could thereby speculate that the number of interventions for non ruptured AAA must increase considerably before it will result in a decline in the number of persons with ruptured AAA. Implementation of screening will obviously contribute to this.

Alterations in population exposure to risk factors must be considered in discussions regarding epidemiologic changes. AAA patients are often males, smokers, elderly and have a positive family history of AAA.^{1, 32, 57, 59} Smoking is probably the strongest modifiable risk factor for AAA. Changes in AAA epidemiology may reflect temporal trends in smoking prevalence in the population of interest. In Sweden, smoking cessation rates have been greater in men than in women,¹⁴¹ which theoretically could lead to alterations in the future gender distribution among AAA patients. In addition, an increase in the proportion of women treated for other manifestations of cardiovascular disease has been reported.^{49, 142} No increase in the proportion of females among patients treated for AAA was observed in study I, which to some extent was unexpected. Only patients treated for AAA were included in study I and no conclusions can be drawn regarding AAA patients admitted due to the disease but not treated.

Rupture

Among patients treated for AAA in Sweden the last decades, a greater proportion of all men were treated for rupture compared to women, 35.1% vs. 31.7% (study I). Since there are no data on patients admitted but not treated in study I, the reason for this difference is not known. Katz et al were the first to report in a population-based study including approximately 40000 patients, that men are more likely to be treated with surgery than women in the event of AAA rupture.¹¹² This gender association interestingly remained after adjustment for age and comorbidities in a regression model. This finding has been confirmed in other studies.^{53, 111, 113, 114} Why a greater proportion of women is declared unfit for surgical intervention, irrespective of age, remains unclear and further studies are necessary.

Women with AAA have a higher rupture risk compared to men.^{5-7, 88} This gender association remains even after adjustment for age, initial diameter, body mass index, height and comorbidities.⁷ Aneurysm diameter is an estimate of the average rupture risk, but may not be an optimal tool for rupture risk predictions for the individual patient. In a study investigating the ratio of the maximum aneurysm diameter and suprarenal aortic diameter as a measure of proportional dilatation,

AAAs of equal diameters represented a greater proportional dilatation in females than males. The ratio of an AAA in men with a diameter of 5.5 cm was comparable to 5.2 cm AAA in women.¹⁴³ Consequently, a threshold of 5.5 cm for treatment may not be appropriate for women.

Several studies have suggested that biomechanical properties play an important role and can offer better predictors of rupture than maximum AAA diameter.⁸⁹⁻⁹¹ Smaller aneurysms do occasionally rupture,^{5, 144} while some aneurysms grow very large without rupture, hence the necessity to predict the AAA rupture risk on an individual patient basis. Study IV is the first biomechanical analysis of AAA with a gender perspective, an attempt to investigate possible explanations for the increased risk of aneurysm rupture in females using detailed FE models. PWS was similar for women and men, whereas PWRR was slightly higher for women. However, a FE analysis is based on both geometrical and biomechanical properties of the AAA. Interestingly, in the FE analysis of the “gender neutral group”, i.e. where female patients received the same aneurysm wall tissue properties as males, no difference in mean PWRR between women and men was found.

It has been reported that ruptured AAAs tend to be less tortuous than non ruptured AAAs.¹⁴⁵ Women are usually described as having a more complex aneurysm anatomy compared to men, especially more complex proximal neck anatomy.¹⁰⁷⁻¹⁰⁹ Considering the small sample size in study IV, more studies within the area must be performed before firm conclusions can be drawn. The results in study IV indicate that solely geometrical properties not explain the previously reported higher rupture risk for female AAA patients compared to males, but rather differences in biomechanical properties. Future studies regarding gender differences in rupture risk for AAA patients should probably more intensely focus on biomechanical aspects.

Heredity

For individuals and society it is of great importance to have knowledge of hereditary patterns of chronic treatable diseases. Familial aggregation of AAA was first described in the 1970s.¹⁴⁶ Reports the last decades have demonstrated a high prevalence of AAA among siblings of AAA patients.^{64, 66, 67} Case-control studies have reported an approximately four-fold increased risk to be affected for FDRs of AAA patients.^{68, 147} Study II is, to our knowledge, the first population-based case-control study covering the topic, including more than 3000 cases and approximately 16000 controls. We found that the relative risk of AAA associated with a positive family history, compared to no family history, was approximately doubled. A recent population-based study, based on data from the Swedish Twin Registry, confirmed that heredity is important for development of AAA.¹⁴⁸ The results in study II show that an organized approach towards familial screening should be developed in order to enhance identification of persons at risk of developing AAA.

Possible gender differences in hereditary patterns have been reported, but the results from these studies are not possible to generalize.^{149, 150} In study III we could demonstrate that the relative risk of AAA associated with a positive family history is doubled regardless of gender.

AAA is a multifactorial disease involving environmental and genetic risk factors. Study II did, however, not address the genetic mechanisms. In summary, in addition to other modifiable or non-modifiable risk factors for AAA, the doubled relative risk associated with heredity should be added to the overall evaluation of persons at risk of developing AAA.

TAA in AAA patients

Several reports have shown that women treated for AAA have an increased standardized mortality ratio compared to men.^{8, 9} Our group has previously reported that the late causes of death for patients treated for AAA, and surviving the first 30 postoperative days, differ between women and men.⁸ Female AAA patients more commonly suffer from aneurysm related death than men. In the analyzed data set including all patients treated for AAA, "aneurysm related death" covered the diagnosis AAA or TAA. Considering that the patients were already treated for AAA, the probability is high that TAA would be the cause of death.⁸ Published reports regarding the prevalence of TAA in AAA patients are limited. Previous studies were not designed to allow conclusion of concurrent TAA in a general population of untreated AAA patients. The main focus in other reports has been on the frequency of previous abdominal aortic repair among patients treated for TAA, which varies between 10-23%.¹⁵¹⁻¹⁵³ In a study of 1104 treated AAA patients, 4% were reported to undergo later repair of a thoracovisceral aortic aneurysm.¹⁵⁴ Study III is unique and also the most comprehensive with respect to assessment of concurrent AAA and TAA. Approximately one quarter of the patients with AAA had a concurrent TAA, mostly located in the descending aorta.

To our knowledge, no consensus document or uniform definitions of normal diameters of the thoracic aorta have been published in recent years. The suggested aneurysm definition of a 50% increase compared to normal diameter (Ad Hoc Committee on Reporting Standards)¹⁸ is associated with difficulties in clinical practice, since the normal diameter is not well defined for the thoracic segment. Some smaller studies have attempted to give reference values.^{23, 155} Wanhainen et al recently presented normal diameters of different aortic segments, based on MRI in women and men 70 years of age,²⁵ those definitions were used in study III.

When using gender specific aneurysm criteria, we found a strikingly high proportion of female AAA patients with a concurrent TAA, 48% compared to 23% in men. The concept of gender specific definitions of TAA are supported by the fact that previous studies have shown that male gender is associated with a larger diameter of the thoracic aorta in healthy adults.^{21-23, 25} A recently published study compared TAA diameter between men and women as a function of relative aortic

size as reflected by aortic size index, which takes into account body surface area. The authors concluded that TAAs of equal diameters represent a larger proportional dilatation in women compared to men.¹⁵⁶

In view of the higher proportion of women among TAA patients than AAA patients, the higher prevalence of TAA in women with AAA than in men demonstrated in study III should not have been so unexpected. Interestingly, this has not previously been reported, nor the prevalence of TAA in AAA patients in general. The traditional separation of the two patient groups, to either being attended by vascular surgeons (AAA) or cardiothoracic surgeons (TAA), probably contributes to the lack of studies within this field.

An increasing number of patients with thoracic aortic pathology are treated both electively and in the emergency situation with endovascular methods, TEVAR.¹⁵⁷ The long term results after TEVAR compared to pharmacological treatment or open repair are still quite unknown.¹⁵⁷⁻¹⁵⁹ The obvious limitation for operability in general for the AAA and TAA patients is high age, apart from severe comorbidity, although some reports indicate acceptable survival rates in octogenarians.¹⁶⁰ The findings in study III indicates that radiological examination of the thoracic segment should be considered for patients with AAA, especially in women. The risks associated with high dosage of radiation must be considered negligible in view of the desired “one time investigation of abdominal and thoracic aorta”.

CONCLUSIONS

- Interventions for non ruptured AAA increased in Sweden the last decades, with an expected rapid increase of EVAR. No increase in interventions for rupture was observed. The male to female ratio in treated patients remained unchanged.
- There is a doubled relative risk of AAA for first degree relatives to patients with the disease. Neither the gender of the index person nor the first degree relative influences the risk.
- Approximately one fourth of AAA patients have a concurrent TAA, mostly located in the descending aorta. Female AAA patients are particularly affected. These findings confirm that possible presence of TAA in AAA patients is clinically important.
- Solely geometrical properties are not likely to explain the higher rupture risk for female AAA patients compared to males. Differences in biomechanical properties are more probable to contribute to the explanation.

FUTURE PERSPECTIVES

The contributing mechanisms for the male predominance in AAA prevalence are not fully understood, and are still the most intriguing research topic. Knowledge of gender differences in AAA patients is rapidly evolving, but it is obvious that future studies are necessary. Two additional topics that should be further highlighted, and probably are related, are the higher rupture risk and possible increased growth rate in female AAA patients compared to males. It is possible that rupture risk estimations based solely on aneurysm diameter are not sufficient, and new tools are required as a complement for individual rupture risk estimations. The last study of this thesis addressed this gender difference from a biomechanical perspective. It would be of great interest to carry this research topic further in a larger study setting. It is possible that individual biomechanical properties in combination with aneurysm diameter could enhance rupture risk estimations in AAA patients and contribute to explain the gender influence on rupture risk. Moreover, investigating pharmacological strategies to decelerate AAA expansion is an exciting possibility. Knowledge of the optimal pharmacological treatment for women and men with AAA could contribute to dilute the association between gender and rupture risk.

The increased risk for FDRs of AAA patients to develop AAA highlights the importance of selective screening program for FDRs in the future. Obviously such screening should include both women and men. Moreover, future care of AAA patients ought to include more thorough investigation of the thoracic segment of the aorta, especially in female patients. Taking the gender difference regarding concurrent AAA and TAA into account, it could be hypothesized that women are more affected by multiple aneurysms than men. A prospective study investigating the occurrence of TAA and aneurysms in other locations e.g. in the popliteal arteries in patients with AAA would be of great interest.

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